From Single-Scale to Multiscale Modelling in Biology

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Abstract Multiscale modelling in biology is used to take into account the complex interactions between the different organization levels in living systems. We review several models, from the most simple to the complex ones, and discuss their properties from a multiscale point of view.

Keywords Multiscale model · master equation · reaction-diffusion equation · hybrid modelling · individual-based modelling · Structured PDE

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Mathematics Subject Classification (2000) 60H10 · 35Q84 · 60J25 · 82C31 · 91B69 · 35K57

1 Introduction

Multiscale modelling first appeared in material engineering problems. Modelers in biology have adapted multiscale techniques to study cancer and other complex biological systems [34,16,35,38,24,29]. Here we present a few approaches to multiscale modelling in biology. We identify desirable properties such as description at many scales and interactions among and between scales. We proceed stepwise, beginning with classical models in mathematical biology, and introducing progressively richer structures that share more of the features of a multiscale model. We begin with the Lotka-Volterra predator-prey equations [20]. We then introduce the FKPP reaction-diffusion equation [25], followed by the Turing equations for pattern formation [36], and the Keller-Segel equations for chemotaxis [21]. We then propose an approach, based on master equations for stochastic processes, to build a multiscale model. We present contemporary approaches for multiscale modelling: individual-based models, hybrid models, and structured PDE models. Examples include multiscale models used to

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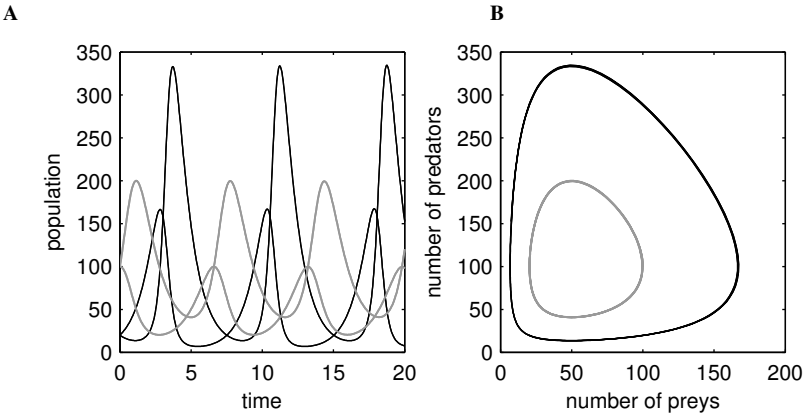

Fig. 1 Lotka-Volterra predator-prey system (1), with $a = c = 1$, $b = 0.01$ and $d = 0.02$, for two different initial conditions: $x_0 = 20, y_0 = 20$ (*black*) and $x_0 = 100, y_0 = 100$ (*grey*). A) Time evolution of preys and predators numbers. B) Solutions shown in panel A lie on distinct, closed trajectories.

probe cancer growth and treatment strategies [23,32,3]; models for the cell cycle [4,11] and cell differentiation [18,6]; and spatial multi-scale models for tissue and cancer growth [15, 12,14,13]. Based on the discussion, we propose two properties any model should possess to be multiscale.

2 From Single-scale to Multiscale Models

Any working definition of multiscale modelling would classify most mathematical models in biology as non-multiscale, or single-scale. We discuss here the scales of four classical models in biology with increasing complexity.

Predator-Prey Interactions. Lotka-Volterra equations are a system of two nonlinear ordinary differential equations describing the interaction between two species, a predator and a prey [20]. Their first use in biology date back to 1925 (Lotka) and 1926 (Volterra). The dynamical variables are the populations (numbers) of preys (x) and predators (y). Preys find enough food at all times, and predators feed on prey. The populations evolve according to the equations

$$x' = x(a - by), \tag{1}$$
$$y' = y(dx - c). \tag{2}$$

(Here and in the following, time derivatives in ODEs are denoted by the symbol $'$ and all coefficient are positive.) At the population scale, equations (1–2) state that the growth rate of the prey population is constant (a) and the death rate of the preys is proportional to the number of predators (by). The death rate of the predators is constant (c) and the growth rate of the predator population is proportional to the prey number (dx). The positive fixed point $(x,y) = (\frac{c}{d}, \frac{a}{b})$ is unstable (it is a center). The predator-prey population oscillate around the fixed point along close trajectories (Fig 1).

This is an example of a population model, and it involves interactions between objects at a lower scale: individuals. Yet this is clearly not a multiscale model. A multiscale model

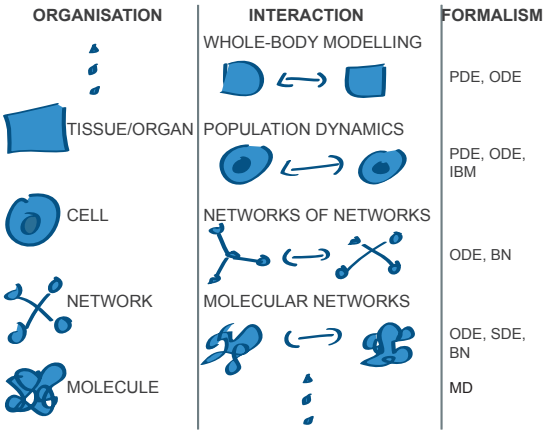

Fig. 2 Organization scales in biology. Single-scale model equations are determined by the interactions at the lower scale. For example, to model a molecular network it is necessary to describe the interaction between molecules. From this point of view, a tissue is a collection of cells interacting together; a cell is a collection of networks interacting together; a molecular network is a collection of molecules interacting together. Scales can go lower (atoms/ions interacting in a single molecule) or higher (organisms interaction in an ecosystem). ODE: Ordinary Differential Equations, PDE: Partial Differential Equations, SDE: Stochastic Differential Equations, IBM: Individual-Based Modelling, BN: Boolean Network, MD: Molecular Dynamics.

should be able to provide information at more than one scale, for instance, on population ("is the wolf population declining?") and on the individual themselves ("which wolves find prey?"). The first question can be answered, while the second one cannot. All the wolves are the same, so are all the hares. What is missing to the predator-prey model is the ability to characterize individuals.

This example shows that two populations with simple interactions can display oscillations in their number (Fig 1). This is not multiscale modelling because there is only one scale, the population, even though the model rests on assumptions on interactions between individuals. Modeling is about describing interactions between single objects. By considering a large number of these objects, we obtain population equations. It turns out that this link between organization at one scale and the interaction at the lower scale is always present (Fig 2).

Reaction-Diffusion Equations. ODEs cannot be multiscale because they do not describe individual objects. Perhaps providing individuals with attributes could help devising a multiscale model. We could endow individual with a spatial position, for instance. Let us have a look at some examples involving a spatial variable x.

The Fisher-Kolmogorov-Petrovskii-Piskunov (FKPP) equation is a reaction-diffusion partial differential equation, introduced by R.A. Fisher in 1937. The equation describes the frequency $\rho(t,x)$ of an advantageous gene in a population located at position x, at time t. Individuals carrying the gene reproduce faster. The growth rate of the frequency ρ is given by a logistic term $r\rho(1-\rho)$. At the same time, individuals carrying the gene move by diffusion ($D\rho_{xx}$). The FKPP reaction-diffusion equation is

$$\rho_t = D\rho_{xx} + r\rho(1-\rho). \tag{3}$$

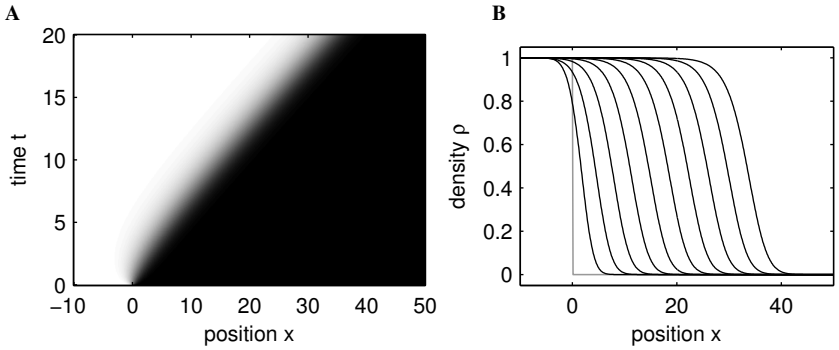

Fig. 3 Solution to the FKPP equation, with $r = D = 1$, and initial conditions $\rho_0(x) = 1$ if $x \leq 0$ and 0 otherwise, and Neumann boundary conditions (no flux). A) Raster plot of the solution $\rho(t,x)$, with increasing values from black to white. B) Solution profiles $\rho(t,x)$ in x for successive fixed times t. It can be shown that the solution is "moving" to the right at a constant speed $c = 2\sqrt{rD} = 2$ [25]. The initial condition is emphasized in grey.

(Subscripts in PDEs denote partial derivatives.) There are two homogeneous solutions to this equation: an unstable one, $\rho(x) \equiv 0$, and a stable one, $\rho(x) \equiv 1$. Equation (3) admits traveling wave solutions of the form $\phi(x - ct)$. The wave $\phi(y)$ moves at a constant speed c, and connects the steady states 0 and 1, the stable state one "invades" the unstable steady state 0 (Fig 3).

As with the Lotka-Volterra equations, the FKPP equation describes a population. Equivalently, the interaction scale is the individuals carrying or not the advantageous gene. Although we do not see any individual, there are differences in gene frequency depending on the location x. If we look at coarse-grained populations living in different locations given by a partition of the space, like villages dotting the countryside, we can characterize each of them by their gene frequency. Not only can we count the villages, but we can distinguish between them. Therefore, we have satisfied our first multiscale model condition: we have a population model with individual objects (the villages) that can be distinguished. We have two scales of description, the number of villages, and how is each village. Nevertheless, the FKPP as a multiscale model is not satisfying. The number of villages is constant, and the gene frequency does not interact with the number of villages.

Pattern Formation. Alan M. Turing introduced this system in 1952 to show how spatial patterns (spatially heterogeneous solutions) could arise from diffusion of chemical substances, when diffusion was thought to lead to homogeneous solutions. In his paper [36], Turing discusses a system of two morphogens regulating each other and diffusing in space. One is an activator and the other is an inhibitor. The activator, u, activates itself and the inhibitor. The inhibitor, v, inhibits itself and the activator. The concentrations of u and v can show spatial instabilities if the diffusion rate of the activator is much smaller than the diffusion rate of the inhibitor. When the activation/inhibition are linear, the equations are

$$u_t = D_u u_{xx} + f_u u + f_v v, \tag{4}$$

$$v_t = D_v v_{xx} + g_u u + g_v v. \tag{5}$$

Again, we can coarse-grain the space x to consider, for instance, cells, located at x, characterized by certain amounts of activator and inhibitors. Spatial instabilities, or Turing patterns, offer an example of lasting heterogeneity, by which cells can be distinguished or

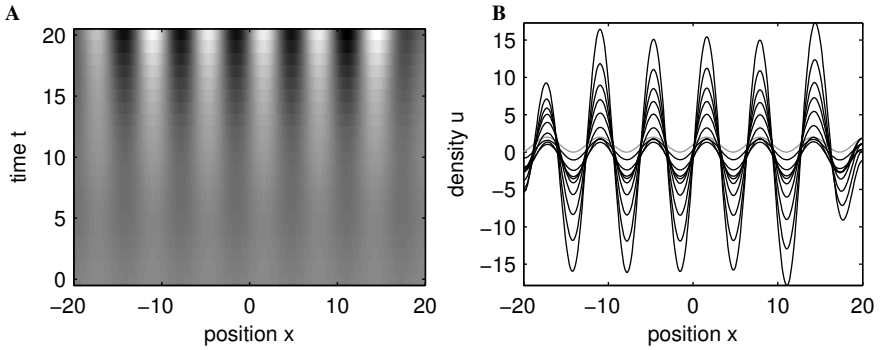

Fig. 4 Solution to the Turing equations, with $f_u = 0.4$, $f_v = -0.5$, $g_u = 1$, $g_v = -0.5$, $D_u = 0.2$, $D_v = 10$, with initial conditions $\big(u_0(x), v_0(x)\big) = \big(1+\sin(x), 1+\cos(x)\big)$ and Neumann boundary conditions (no flux). A) Raster plot of the solution $u(t,x)$, with increasing values from black to white. B) Solution in x at successive, fixed times. The initial condition is emphasized in grey.

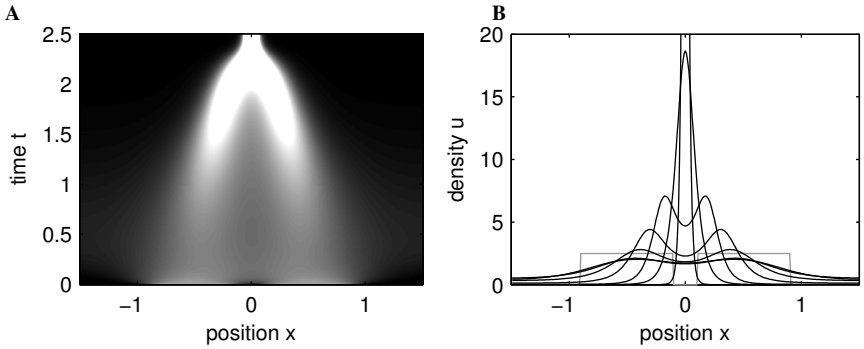

Fig. 5 Solution to the Keller-Segel equations (6–7), with $d = 0.5$, $\varepsilon = 0.05$, $a = 0.1$, with initial conditions $\big(u_0(x), v_0(x)\big) = 2.5\big(\mathbf{1}_{[-0.9,0.1]} + \mathbf{1}_{[0.1,0.9]}, 0\big)$ and Neumann boundary conditions (no flux). A) Raster plot of the solution $u(t,x)$, with increasing values from black to white. White indicates $u \geq 4.0$. B) Solution in x at successive, fixed times. The initial condition is emphasized in grey. Solution at $t = 2.5$ is out of bound.

differentiated (Fig 4). Turing equations provide the first model to show how a complex pattern at the tissue level can be generated by interaction between molecules, two scales down, but suffer from the same shortcomings as the FKPP equation: cells are introduced artificially and they do not interact.

Chemotaxis. In the multiscale interpretation of the Turing system, cells are static objects. It would be better is they could move and interact, for instance. Chemotaxis is the phenomenon by which cells move according to concentration gradients in their environment. They could be attracted by food, or repelled by poisons. If the cells themselves secrete chemotactic molecules, we can describe the movement of the cells by a model Keller and Segel developed in 1970 [21],

$$u_t = d u_{xx} - (u v_x)_x, \tag{6}$$

$$v_t = \varepsilon v_{xx} + u - a v. \tag{7}$$

The Keller-Segel equations include two scales: cell density (u) and molecule concentration (v). Interaction between cells is based on the chemoattractant concentration they

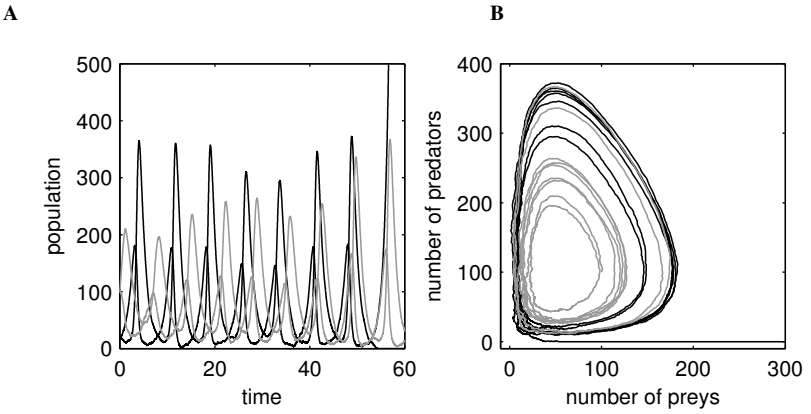

Fig. 6 Two realizations of the stochastic process given by the Langevin version of the Lotka-Volterra system: $x' = x(a-by) + e\xi(t)$ and $y' = -y(c-dx) + f\xi(t)$, for two different initial conditions: $x_0 = 20, y_0 = 20$ (*black*) and $x_0 = 100, y_0 = 100$ (*grey*). Parameters are are the same as simulations shown in Fig 1, $a = c = 1$, $b = 0.01$ and $d = 0.02$. The noise $\xi(t)$ is a Gaussian white noise with standard deviations $e = f = 3$. Absorbing boundary conditions were imposed at $x = 0$ and $y = 0$. A) Time evolution of preys and predators numbers. In one case (*black*), the predator goes extinct at around $t = 55$, leaving the prey population to grow exponentially. B) Solutions shown in panel A wander around. The black preys grow exponentially once the predators are extinct (*horizontal trajectory at* $y = 0$).

produce (Fig 5). Yet, the two scales are not nested, they live in the same world. Cells and chemoattractant are modelled at the same level, like the predator and the prey in the Lotka-Volterra model. We do not have yet a multiscale model.

3 Master Equation-Based Models

The Langevin Equation and the Fokker-Planck Equation. To build a multiscale model, we consider $y(t) \in \mathbb{R}$ the state of a system at time t at a particular scale. If we describe a single cell, y could be mRNA, protein levels, cell mass or gene expression profile. If we describe a population, y could be numbers of quiescent cells, stem cells, differentiated or tumour cells. We assume that y fluctuates around a value given by the nonlinear deterministic system $y' \simeq F(y)$. We add noise term to get a nonlinear Langevin equation [37],

$$y' = f(y) + g(y)\xi(t). \tag{8}$$

The noise component $\xi(t)$ is usually a white noise, that is, a time-uncorrelated noise with zero mean and finite variance, often chosen Gaussian. The associated Fokker-Planck equation for the probability density of the state y at time t is

$$P_t(y,t) + [f(y)P(y,t)]_y = \frac{1}{2}[g(y)^2 P(y,t)]_{yy}. \tag{9}$$

Fokker-Planck equations and Langevin equations are mathematically equivalent formulations [37]. It is also possible to consider Fokker-Planck and Langevin equations in many variables $y \in \mathbb{R}^n$. As an example, we add a noise term to the Lotka-Volterra system (1–2), which is sensitive to small perturbations. The new Langevin system displays behaviour different from the Lotka-Volterra (Fig 6). In particular, population can now go extinct.

The Master Equation. Langevin equations can be used to simulate Markov processes. Markov processes are memoryless stochastic processes, and the probability density function of y at time t, $P(y,t)$ can be expressed as a differential equation local in time but nonlocal in space Γ.

$$P_t(y,t) = \int_\Gamma \{W(y|y')P(y',t) - W(y'|y)P(y,t)\}dy'. \tag{10}$$

Equation (10) is a master equation. The master equation is a gain-loss equation for the probability of each state y. (The Fokker-Planck equation is a special kind of master equation used as an approximate description of a Markov process in which jumps are small and the nonlinearities are smooth.) As an illustration of the master equation approach, we study a model in which cell differentiate by diffusing (i.e. non-directed random movement) into a differentiation space $y \in \mathbb{R}$ [18]. The cell density $n(y,t)$ obeys an equation derived from a master equation,

$$n_t(y,t) = \int_\Gamma p(y|y')R(y')n(y',t)dy' - R(y)n(y,t) + r(y)n(y,t). \tag{11}$$

The distribution $p(y|y')$ of jumps in the differentiation space is Gaussian, with a nonlinear, space-dependent variance $\sigma^2(y')$. The rate of jumps is given by $R(y)$, which is assumed to be correlated to the cell proliferation rate $r(y)$. The differentiation domain $\Gamma = \mathbb{R}$. The associated Fokker-Planck-like equation is found by calculating the first two jump moments [37]. The first jump moment, $\int_\Gamma rp(y+r|y)R(y)dr = 0$, vanishes, and the second moment, $a_2(y) = \int_\Gamma r^2 p(y+r|y)R(y)dr = R(y)\sigma^2(y)$. The Fokker-Planck-like equation associated to equation (11) is then

$$n_t(y,t) = \frac{1}{2}\left\{R(y)\sigma^2(y)n(y,t)\right\}_{yy} + r(y)n(y,t).$$

Denote by $N_A(t)$ the number of cells with $y \in A$, where $A \subseteq \mathbb{R}$ is a subset of cells of interest: $N_A(t) = \int_A n(y,t)dy$. We introduce a logistic growth in the following way:

$$n_t(y,t) = \frac{1}{2}\left\{R(y)\sigma^2(y)n(y,t)\right\}_{yy} + r(y)\left(1 - \frac{N_A(t)}{K}\right)n(y,t). \tag{12}$$

K is the carrying capacity for population A. Equation (12) is not Fokker-Planck equation anymore since it includes a nonlinear population growth term. Cell number is regulated at the cell population scale through the term $N_A(t)$, while the single-cell scale defines how cells move in Γ. The associated single-cell Langevin equation is $y' = \sqrt{R(y)}\sigma(y)\xi(t)$. The Langevin equation only describes part of equation (12):cell movement in Γ. Equation (12) has many desirable properties of a multiscale model. It describes a system at two organization scales: the cell (with $y \in \Gamma$) and the population (with $N_A(t)$), and the interaction between the two scale through the logistic term. The two scales are nested, N_A is formed directly by the density n.

4 Individual-Based Models

Individual-based modelling (IBM), or agent-based modelling, has been used in computer science, social sciences, ecology and more recently in biology [30]. Models are composed of many agents who can make decisions, learn and adapt, and interact with other agents and

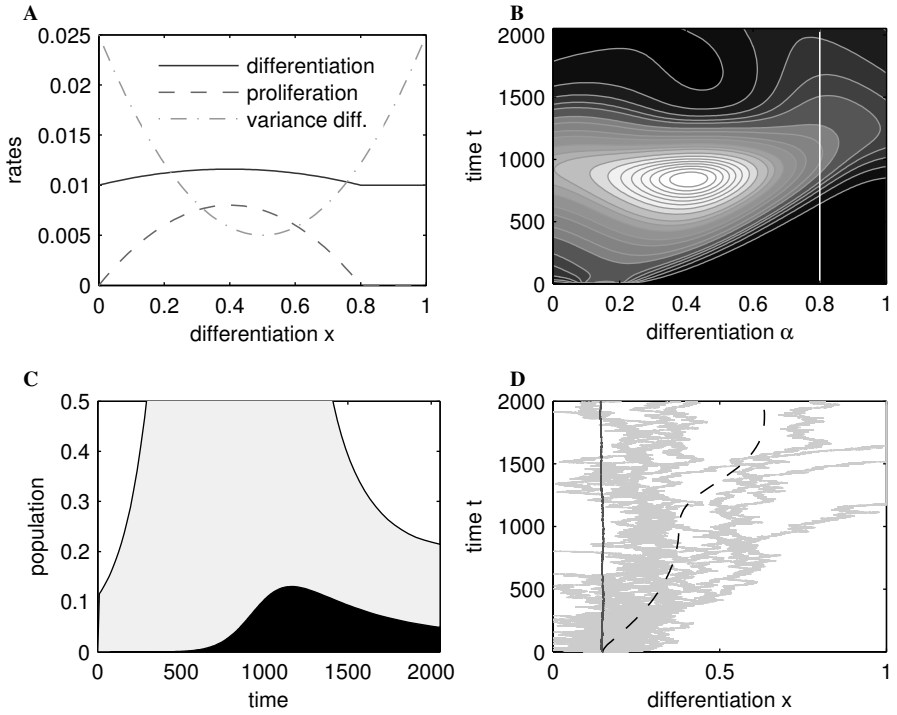

Fig. 7 Solution to the multiscale reaction-diffusion equation (12) derived from the Fokker-Planck equation. The domain is $\Gamma = [0,1]$, and $A = [y_N, 1]$. Functions are $R(y) = r_0 + r_1 r(y)$, $r(y) = 4r_{max} y(1 - y/y_N)\mathbf{1}_{[0,y_N]}$, $\sigma^2(y) = s_0 + 4s_1(y - 1/2)^2$. Parameter values are $r_0 = 0.01$, $r1 = 0.20$, $r_{max} = 0.01$, $s_0 = 0.005$, $s_1 = 0.02$, $K = 0.05$, $y_N = 0.8$. A) Rate functions. B) Raster plot of the solution $n(y,t)$, with increasing values from black to white. C) $N_{[0,1]}(t)$ (*grey*) and $N_A(t)$ (*black*). D) Some realizations of Langevin equation (*grey*) and their mean (*black*) compared to the mean differentiation value of the solution $n(y,t)$ (*dashed line*).

the environment. They are not necessarily multiscale. However, they are flexible enough to allows a multiscale description.

Drasdo and colleague have developed a methodology for simulating proliferating cells [13]. Cells are modelled as oriented, deformable spheroids that can move, rotate, change shape, grow in volume and divide into two daughter cells. Cells interacts mechanically and biochemically through membrane surface molecules. Internal properties of the cell regulate how fast cells grow and divide, and which type of surface molecules are expressed. Although simulations can be computationally costly, this kind of modeling can reproduce many of the features of a growing tissue. This type of single-cell-based model has had many applications: epithelium [13,15], tumors [12,31] and more recently liver regeneration [17]. A related method has been proposed [26].

5 Hybrid Continuous-Discrete Models

This is a popular approach to multiscale modelling, in which cells are discrete entities and molecular concentrations are given by continuous equations. The space contains a coarsed-grained lattice. At each node, one or many cells can be present. Each cell is represented individually and is endowed with relevant property: shape, intracellular state, cycling status,

mutation, etc. Cells can move, replicate, die and interact with other cells, directly, or via an extracellular medium.

Ribba and colleagues proposed a multiscale model for cancer growth, with the purpose of optimizing therapeutic irradiation protocols [32]. The model incorporates gene regulation, cell kinetics, tissue dynamics, macroscopic tumor evolutions and radio-sensitivity dependence on cell cycle phase. Intracellular interactions are modelled by a boolean network. The state of the boolean network determines how cells progress in the cell division cycle and their fate. Cell can either divide, stop in a quiescent phase, or die by apoptosis. Cell cycle progression, arrest or death is monitored by a cell cycle status. Cell are laid on a lattice and are subject to a changing environment, consisting in the local cell density and the oxygen concentration. Cell fate depends on the local environment. On a tissue level, a fluid dynamics model is used to describe cell movement. Radiation therapy affects the molecular network, which in turn affect cell fate, and tumor progression.

Although the model is too complex to reproduce here, we can identify the multiscale features of the model. The model spans three organization scales: genetic/molecular networks, cells and tissues and interactions between scales are modelled explicitly.

Anderson and colleagues developed a multiscale model for tumor morphology and phenotypic evolution, in which phenotypic mutations and selection drive the tumor morphology evolution [2,3]. Discrete cell are laid on a square lattice. Cells are characterized by a life cycle governing proliferation and death, and by a phenotype with traits describing key properties of cancer cells like propensity to proliferate or cell-cell adhesion. Cell can undergo phenotypic mutations that will affect their ability to proliferate and move. Because resources (space, oxygen) are limited, phenotypic selection operates and defines the dynamics of tumor evolution. Oxygen and extracellular matrix concentrations are modelled with PDEs.

More recently, we have developed a hybrid multiscale model cell proliferation and differentiation [23,6]. Cells are modelled as discrete objects (IBM). Cell behaviour depends on continuous intracellular and extracellular processes. The model was developed to simulate the evolution of immature blood cells in the bone marrow. In the version proposed by Kurbatova et al. [23], cell differentiation, self-renewal, and apoptosis are determined by an intracellular network, and by extracellular regulation. The resulting multiscale model was used to probe the effect of different chemotherapeutic treatment schedules on leukemic and normal cells.

A feature of hybrid models is their ability to reproduce relevant biological phenomena, including spatial and intercellular heterogeneities. To illustrate the potential of hybrid models, we show how discrete cells with molecular network of circadian clocks can communicate and synchronize their clocks (Fig 8). The circadian clock model oscillate with a period of around 24h only if the cells are properly coupled [5].

6 Structured PDE Models

Population models structured by molecular content are becoming increasingly popular. Structured equations can be derived from Fokker-Planck equations without noise (for instance, equations (8) and (9) with $g = 0$).

Doumic presented and analysed a model structured by age a and molecular content x [11]. The equation describes the evolution of the density $n(t,a,x)$ at time t, of cells aged a with molecular content x. The evolution of the molecular content x, the structure, and the age are given by a system of ODEs, $x' = F(a,x)$ and $a' = 1$. Cells are lost with a rate

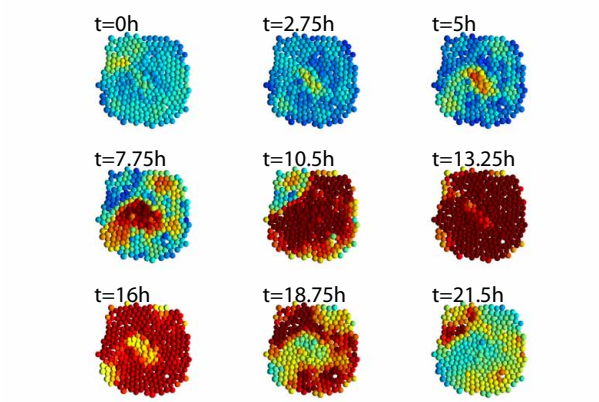

Fig. 8 Synchronization of circadian clocks in 300 cells induced by cell-cell contact interaction. Cells (*small spheres*) move freely, but tend to stay in contact with each other, and express a clock marker (*blue: low, red: high levels*). Details on the intracellular network and coupling can be found in [5].

Table 1 Model scales and formalisms. ODE: Ordinary Differential Equations, PDE: Partial Differential Equations, Age: Age-structured model, Phase: Phase-structured model, Phen.: Phenotypic space with random mutations, IBM: Individual-Based Modeling, CA: Cellular Automaton, BN: Boolean Network.

Model	Organization Scale			
	Mol. Network	Cell Kinetics	Tissue Dynamics	Ext. Space
Master Eq.	ODE/SDE	Phase	PDE/FP-based	N/A
Ribba [32]	BN	Phase	PDE	PDE
Drasdo [15]	N/A	Age	IBM	N/A
Kurbatova [23]	ODE	Phase	IBM	PDE
Anderson [3]	N/A	Phen./Phase	CA	PDE
Bekkal [4], Doumic [11]	ODE	Phase/Age	PDE	N/A

$B(a,x)$ and a boundary conditions at $a=0$ defines the birth rate of new cells. The structured equation is a birth-death transport equation describing how cells move, die and are born in the age/structure space (a,x).

$$n_t + n_a + \{F(a,x)n\}_x + B(a,x)n = 0,$$
$$n(t,a=0,x) = 2\int_0^\infty \int_\Gamma b(a,x,y)n(t,a,y)dyda.$$

This system of equations involves two scales: the molecular scale given by the equation $x' = F(a,x)$ and the population scale, with the death term $B(a,x)$ and the boundary condition. This model is a simplified version of a population model structured by cyclins with explicit cell cycle phases [4].

7 Discussion and Conclusion

We have presented here several approaches to multiscale modelling, from master equation-based approaches to individual-based and hybrid models to structured models. Stochastic and multiscale formalisms share many attributes. Depending on the point of view, the same equation can describe a stochastic or a multiscale phenomenon, as with the Fokker-Planck equation. In both multiscale and stochastic models, there are at least two distinct scales.

The choice of the scales is left to the modeler, but many models incorporate scales ranging from molecules to the tissue, with the cell as the fundamental modelling unit (Table 1). One consequence of multiscale modelling is the need to have a detailed but simple description of the intracellular dynamics, with mechanisms to create heterogeneity between cells. Stochastic processes are compatible with the multiscale framework developed here and have been well studied in the context of intracellular networks [22,27,19,28,33]. In a recent review, Byrne and Drasdo discussed the merits of individual-based models and continuum models of cell populations [7]. We could cover only a small part of the multiscale modelling literature. More approaches to multiscale modelling and examples of applications can be found in recent books [8,10,9].

Based on the discussions presented here and elsewhere [1], we propose list of properties a computational or mathematical model should possess to be a multiscale model

- *At least two nested organization scales*. We should be able to distinguish attributes of objects at each scale. The lower scale should be imbedded into the higher scale. Coupled equations for cell densities and molecular concentrations like equations (6)–(7).
- *Interaction between and among scales*. Emerging behaviour (higher scale) of interacting particles (lower scale) is not sufficient, the emergent behaviour should interact with the particles themselves.

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